REMARKS

Claims 1-27 and 30-36 are pending in the above-identified application. The amendment to the specification is made to correct an informality, removing browser-executable code to conform to M.P.E.P. § 608.01. Accordingly, the amendment does not raise an issue of new matter and entry thereof is respectfully requested. Applicant has reviewed the Office Action mailed February 23, 2003, and respectfully traverses all grounds for rejecting the application for the reasons that follow.

Rejections Under 35 U.S.C. § 112

Claims 1-27 and 30-36 remain rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement allegedly because it would be unpredictable to practice the invention as claimed. The Office asserts that undue experimentation would be required allegedly because the transgenic mouse must express the claimed construct such that the transgene is expressed in the rod outer segment (ROS) in sufficient amounts for purification or for performing drug screens. In this regard, the Examiner maintains that Ryan et al. describes transgenic expression to be unpredictable and cites passages from Ryan et al. that allegedly support this contention. Lim et al. is again cited for supporting the assertion that that rhodopsin knock-out mice may be lethal and additionally because knock-out mice that do not express rhodopsin fail to form outer rod segments. Similarly, Holschneider et al. is again cited to support the assertion that transgenic expression varies with particular gene constructs. Finally, the Examiner also appears to assert that the transgenic mice described in the application lack a real world utility allegedly because there are less expensive alternative methods to produce polypeptides of interest.

The Office acknowledges that routine experimentation, even if it is time consuming, does not constitute undue experimentation. *Johns Hopkins Univ. v. CellPro, Inc.*, 152 F.3d 1342, 1360 (Fed. Cir. 1998) (Applicant's response filed October 30, 2003, at page 9). The Office further acknowledges that the application teaches a number of different methods for making and testing the transgenic mice encompassed by the claimed invention. However, the Office maintains that Ryan et al. allegedly supports that the amount of experimentation required to make transgenic mice that properly express the protein of interest would not be considered routine. Applicant previously pointed out that Ryan et al. is inapplicable to the claimed

invention because it is directed to transgenic expression by random insertion of the transgene rather than to homologous recombination at a rhodopsin gene. The Office alleges that this argument is unpersuasive because the proper expression of the transgene in the ROS of the eye is required as a phenotype and Ryan et al. allegedly indicates that such expression is unpredictable.

The excerpts quoted from Ryan et al. appear to exemplify certain drawbacks that can occur when the method of introduction of a transgene is random insertion into a host genome. Ryan et al. does not state or suggest that expression is unpredictable. Rather, Ryan et al. states that transgenic expression by random genome insertion is associated with certain disadvantages such as "differences in transgene copy number and position of integration in the genome" and "differences in baseline phenotypes" reported in different genetic backgrounds (Office Action at page 5, *quoting* Ryan et al.). Further, the reported disadvantages in Ryan et al. are stated in context of constructing a animal model that "perfectly emulate[s] a gene at its normal location in the genome" (Office Action at page 5, *quoting* Ryan et al.).

Initially, Applicant respectfully points out that production of an animal model that perfectly emulates a gene at it's normal locus differs from the purpose of the claimed invention. As described, for example, at page 5, lines 4-7, one purpose of the claimed invention is to express and purify large amounts of transgenic polypeptides expressed in the rod outer segment (ROS). Additionally, even if a purpose of the claimed invention was to emulate expression of a gene at its normal location in the genome the constructs, cells and mice of the claimed invention place the transgene in a normal locus for rhodopsin expression because the invention claims flanking sequences which effect homologous recombination with the host rhodopsin gene. Therefore, the claimed flanking sequences avoid the deficiencies described by Ryan et al. and render its description inapplicable as support for unpredictability.

As Applicant pointed out in its previous response, any description in Ryan et al. regarding unpredictability is associated with random transgenic expression. The homologous recombination at a rhodopsin gene is distinct in both the method of insertion and in the obtained results. The application teaches and the invention claims gene targeting constructs flanked by 5' and 3' DNA sequences that are homologous to the mouse rhodopsin gene as well as a cell and a

mouse produced by the claimed constructs. The homologous flanking sequences result in homologous recombination at the mouse rhodopsin gene. For example, the application teaches:

> A flanking nucleotide sequence that is "homologous" to a rhodopsin gene sequence refers to a nucleotide sequence having sufficient identity to a rhodopsin gene sequence to allow for homologous recombination between the nucleotide sequence and an endogenous rhodopsin gene sequence in a host cell.

Application at page 15, lines 21-26. The application further teaches:

> The flanking homologous DNA sequences are of sufficient length for homologous recombination to occur between the targeting construct and an endogenous rhodopsin gene in a cell when the construct is introduced into the cell.

Application at page 14, lines 21-25.

Therefore, the application teaches homologous recombination of a transgene at a host rhodopsin gene location using the claimed gene targeting constructs of the invention. Because introduction of a transgene into a host genome occurs at a specific site the claimed cell and mouse produced using the claimed constructs is distinct from those produced using random insertion as described by Ryan et al. Accordingly, the claimed cell and mouse are not fraught with disadvantages such as variable transgene copy number and position of integration observed using random insertion methods which led to variation in expression levels described by Ryan et al.

Additionally, the application teaches and the claims are directed to a gene targeting construct, a cell and a mouse produced from the claimed construct that results in the homologous recombination or site specific recombination of the transgene at the rhodopsin gene locus in such a manner that expression will occur. Therefore, the assertion by the Office that the transgenic mouse of the invention "require[s] the *the proper expression of the transgene in the ROS of the eye*" is, in fact, claimed. Office Action mailed February 23, 2004, at page 6 (emphasis original). Accordingly, Applicant is not claiming all transgenic mice and has excluded those embodiments that fail to produce expressed transgenic polypeptide in the ROS.

For example, the claims are directed to a transgene flanked by 5' and 3' DNA sequences that are homologous to and which homologously recombine with the mouse rhodopsin

gene to result in an operable association between the transgene and a rod-specific regulatory sequence. Operable association of the recombined transgene permits expression of the newly introduced transgene. The application teaches that homologous recombination results in an operable association with rod-specific regulatory sequences when it states:

> To provide for transcription and, ultimately, translation, of the transgene in rod cells, the construct is designed such that the transgene will be operably associated with rod-specific regulatory sequences following homologous recombination with a rhodopsin allele. As used herein, the term "operably associated" indicates that the rod-specific regulatory sequences and the transgene are positioned in such a manner so as to permit transcription of the transgene under the control of the rod-specific regulatory sequences.

Application at page 15, line 23 through page 16, line 2.

Accordingly, the application teaches and the claims are directed to a cell and a mouse that has the transgene homologously recombined at a rhodopsin gene locus and which is operably associated with rod-specific regulatory sequences. Therefore, the invention claims only those cells and mice that have an operable association with host regulatory sequences so as to permit transcription and expression of the transgene.

The Office maintains that Lim et al. further supports the assertion that the amount of experimentation required to make the transgenic mice that properly express the protein of interest would be unpredictable. The Office states that "Lem explicitly teaches that the rhodopsin knock-out mouse has a degenerative eye disorder wherein the 'rod outer segments failed to form.'" Office Action mailed February 23, 2004, at page 7 (emphasis and citation omitted). The Office concludes that although a ROS targeted transgenic mouse may be capable of expressing the transgene in the early part of life, it appears to be impossible, absent evidence to the contrary, that the resulting polypeptide would be localized to the ROS.

Applicant respectfully disagrees with the Office's interpretation of Lem et al. As pointed out in Applicant's previous response, Lem et al. expressly describe the normal development of retinas in mice in a rhodopsin-null mouse, when Lem et al. state:

> Retinas in mice lacking both opsin alleles <u>initially developed normally</u>.

Abstract at page 736 (emphasis added). Further with respect to normal development of retinas with rhodopsin knock-out mice, Lem et al. also describe, for example, that retinal degeneration was not complete by 90 days after birth. Therefore, in these mice, there was some rod segments even after 90 days (page 739, column 2). Applicant could thus remove the retina from animals before the degeneration stated by Lem et al. occurs. In particular, retinas could be collected in mice well prior to 90 days of age, when retina development is complete and significantly ahead of any observed retina degeneration by Lem et al.

Additionally, Lem et al. expressly describe a solution to overcome any lack of normal development of retinas in rhodopsin knock-out mice. In this regard, Lem et al. describe that any later stage retinal development problems can be circumvented by constructing a single rhodopsin gene knock-out instead of both alleles. For example, Lem et al. state:

> Retinas from mice with a single copy of the opsin gene developed normally, and rods elaborated outer segments of normal size but with half the normal complement of rhodopsin. Photoreceptor cells in these retinas also degenerated but did so over a much slower time course.

Abstract at page 736, *see also* page 741, col. 1, para. 3 (concluding "[o]lder [hemizygous] animals exhibited a very slow retinal degeneration).

In this regard, about half of the experimentation and discussion in Lem et al. is directed to corroborating that single rhodopsin knock-out or hemizygous mice generate functional retinas. Therefore, in contrast to the assertions by the Office, Lem et al. fail to support unpredictability of rhodopsin knock-out mice. Specifically, Lem et al. describe the normal development of double allele rhodopsin knock-out mice. Lem et al. further provide guidance that there is a period of time after which that these mice may develop a disorder in which the ROS degenerates. Lem et al. also describe a solution to overcome such degenerative cases where the solution is to produce as single allele rhodopsin knock-out instead of both alleles. Further, Lem et al. describe that the single allele knock-out mice produce functional retinas. Accordingly, Lem et al. provide detailed guidance for the successful production of rhodopsin knock-out mice and fails to support unpredictability of transgenic animals as asserted by the Office.

The Office maintains that Holschneider et al. similarly supports the assertion that the amount of experimentation required to make transgenic mice that properly express the protein of interest would be unpredictable. In response to Applicant's response, the Office reasserts Holschneider et al. allegedly for the same reasons why Ryan et al. was cited, because the claimed transgenic mouse must have a phenotype corresponding to the proper expression of the transgene and localization to the ROS.

Applicant maintains that Holschneider et al. similarly is inapplicable to the claimed invention because the application describes and claims the construction of a transgene encoding polypeptide having a ROS target signal flanked by sequences for homologous recombination that is operable association with a rod-specific regulatory signal. Holschneider et al. are concerned with observing changes in phenotype. As described previously, the application teaches and the claims are directed to a gene targeting construct, a cell and a mouse produced from the claimed construct that results in the homologous recombination or site specific recombination of the transgene at the rhodopsin gene locus in such a manner that expression will occur. Therefore, Applicant is not claiming all transgenic mice. Rather, Applicant is claiming a gene targeting construct, and a cell and a mouse produced from such construct, containing a transgene encoding a polypeptide having a rod outer segment (ROS) targeting signal where the transgene is flanked by sequences homologous to the mouse rhodopsin gene that effect homologous recombination to result in an operable association between said transgene and a rod-specific regulatory sequence. Because Applicant claims an operable association, the claims exclude those embodiments that fail to produce expressed transgenic polypeptide in the ROS. Accordingly, Holschneider et al. and the assertion that a phenotype requiring transgene expression fails to provide an adequate basis for lack of predictability of the claimed invention.

The Office newly alleges that the transgenic mice described in the application lack a real world utility allegedly because there are less expensive alternative methods to produce the polypeptides of interest.

Applicant respectfully submits that the claimed invention provides a real world utility. The application teaches that the expressed transgenic polypeptides and transgenic mice that produce them are useful for the production of large amounts of polypeptide applicable, for

example, in the design of drugs and preparation of agonists or antagonists. For example, the application teaches:

> The trangenic polypeptides expressed in the rod outer segment (ROS) membranes thus comprise a large percentage of the total ROS membrane protein content, and can be readily purified in large amounts. The transgenic polypeptides are also substantially homogenous in their post-translational modifications. Therefore, polypeptides produced by the invention animals and methods are useful for structural studies to elucidate their molecular mechanisms and ligand interactions, thereby providing useful information for drug design. The ROS membrane-expressed proteins are also useful in other applications known in the art for which high quality protein preparations are required or advantageous, including functional studies; screening for ligands, agonists and antagonists; preparation of antibodies; and preparation of pharmaceuticals.

Application at page 5, lines 4-19. Applicant respectfully points out to the Office that drug design and the identification of agonists and antagonists and the preparation of pharmaceuticals are real world utilities.

The real world utility of Applicant's claimed invention has additionally been independently recognized by others. Attached is a declaration by Dr. Juan Ballesteros, Vice President of Research, Novasite Pharmaceuticals, evidencing the recognition by others that the claimed invention is useful. The declaration attests that the assignee of the claimed invention has received two Small Business Innovation Research (SBIR) awards recognizing the commercial value of the research. Additionally, the declaration also attests that the claimed invention has been licensed for the specific purpose of producing large quantities of transgenic polypeptide. In light of this independent recognition of the commercial utility of the claimed invention, the assertion of a lack of a real world utility is moot and withdrawal of this ground of rejection is respectfully requested.

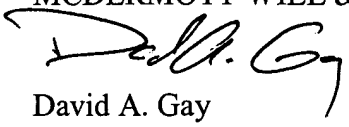
CONCLUSION

In light of the remarks herein, Applicants submit that the claims are now in condition for allowance and respectfully request a notice to this effect. The Examiner is invited to call the undersigned attorney if there are any questions.

To the extent necessary, a petition for an extension of time under 37 C.F.R. 1.136 is hereby made. Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to Deposit Account 502624 and please credit any excess fees to such deposit account.

Respectfully submitted,

MCDERMOTT WILL & EMERY LLP



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